IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Kei Roger Aoki, et al.	Examiner: Anish Gupta
Serial No.: 10/726,904	Group Art Unit: 1654
Filed: December 2, 2003	Confirmation No.: 4172
For: USE OF THE NEUROTOXIC COMPONENT OF A BOTULINUM TOXIN FOR TREATING A SPASTIC MUSCLE	

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APPELLANTS' REPLY BRIEF TO EXAMINER'S ANSWER

Appellants maintain the Appeal and, in response to the Examiner's Answer mailed on December 24, 2008, hereby submits this Reply Brief pursuant to 37 C.F.R. § 41.41(a).

Grounds of Rejection to be Reviewed on Appeal

Rejection 1: Priority under 35 U.S.C. § 120 to parent applications U.S. Serial Nos. 08/173,996 and 08/627,118 has been denied. The Examiner asserts that the parent applications do not meet the "how to use" prong of enablement under 35 U.S.C. § 112, first paragraph, for the pending claims.

Rejection 2: Claims 1-2, 4-5, 29, 47, 63 stand rejected under 35 U.S.C. § 103(a) as obvious over Balkan *et al.* (*Annals of Ophthalmology* 1991; 23(9): 326-333) or Han *et al.* (*Journal of Pediatric Ophthalmology and Strabismus*, 2001; 38(2): 68-71) in view of Tse *et al.* (*Eur. J. Biochem.* 1982; 122(3): 493-500), Kohl *et al.* (*Movement Disord.* 2000; 15(Suppl 3): 165) and Aoki *et al.* (U.S. Patent No. 6,113,915).

Claims 1-2, 4-5, 29, 47, 63 also stand rejected under 35 U.S.C. § 103(a) as obvious over Balkan *et al.* (*Annals of Ophthalmology* 1991; 23(9): 326-333) or Han *et al.* (*Journal of Pediatric Ophthalmology and Strabismus*, 2001; 38(2): 68-71) in view of Kohl *et al.* (*Movement Disord.* 2000; 15(Suppl 3): 165) and Aoki *et al.* (U.S. Patent No. 6,113,915) and Aoki *et al.* (U.S. Patent Publication No. 2001-018415).

Arguments on Reply

The present Reply Brief addresses points raised in the Examiner's Answer in order to clarify certain issues or advance the Appeal process. Arguments that were presented in the Appeal Brief filed July 2, 2008 that are not addressed or further developed herein are expressly maintained.

I. Rejection Under 35 U.S.C. § 120 Denying Priority For Lack Of Enablement

The Examiner has denied claims 1-2, 4-5, 29, 47, 63 the benefit of priority under 35 U.S.C. §119 to parent applications U.S. Serial Nos. 08/173,996 ("the '996 parent application") and 08/627,118, alleging that the parent applications do not enable the claims under 35 U.S.C. § 112, first paragraph.[1] As Appellants indicated in the Appeal Brief, since the present application does not claim benefit of priority to either a foreign or provisional application, the issue is properly directed to whether the presently pending claims are entitled to benefit of priority under 35 U.S.C. §120, not under 35 U.S.C. §119.

In the Examiner's Answer, and as discussed below, the Examiner has disregarded essentially all the evidence Appellants have provided, and instead has placed dispositive weight on one section of a single reference that was cited in the context of an obviousness rejection as teaching away from the claimed methods. Moreover, the Examiner has erroneously and repeatedly misquoted Appellants' statements, including statements regarding that single reference, despite Appellant's repeated efforts to correct the record.

Both the law and the facts are contrary to the Examiner's position, and Appellants respectfully request that the Board reverse this rejection.

[1] The '118 application is a continuation of the '996 application and the disclosures are thus identical. Although the comments in this Reply Brief regarding priority are directed to the earlier-filed '996 application, it will be understood that priority to both the '996 and the '118 parent applications is being sought.

A) The Enablement Rejection is not Based on the Evidence as a Whole

In his Answer, the Examiner asserted that:

> "in determining a non-enabling disclosure of the parent application, the nature of the invention, the state of the prior art, and the level of skill in the art were all considered."

Examiner's Answer at page 14, last paragraph. The Examiner also asserted that Appellants had acknowledged as much in a Response dated December 20, 2007, and quoted Appellants as acknowledging that the non-enablement rejection was premised:

> "on the fact that the specification [parent] did not provide ample guidance on 'how to use' the neurotoxic component in a clinical setting... Applicants did not provide any guidance to one of ordinary skill in the art how one could avoid the problems associated with purified botulinum toxin component... as indicated by Schantz *et al.* the teachings of complexed toxin could not be utilized [for] purified botulinum toxin since the purified portion is so labile that it would not be used in clinical settings."

Examiner's Answer at paragraph spanning pages 14 and 15.

The quote the Examiner attributes to Appellants, however, is **the Examiner's own statement from an earlier Office Action**, which Appellants were quoting as a preface to addressing the rejection. Response of December 20, 2007 at pages 4-5. In fact, Appellants maintained in the December 20, 2007 Response, and continue to maintain, that the Examiner has disregarded nearly all of the objective evidence that Appellants have put forward. Appellants did not acknowledge that the enablement rejection was proper, or that it was based on the evidence as a whole. Intentionally or not, the Examiner has mischaracterized Appellants' quotation of the Examiner as Appellants' own stated position during prosecution. Appellants object to such a mischaracterization, especially given that the Examiner is attempting to use Appellants' Response to buttress an already improper enablement rejection.

B) Appellants Have Provided Evidence Demonstrating Enablement

Appellants have provided a wide range of evidence, including evidence from the specification, evidence from published scientific articles, and evidence from sworn declarations of distinguished experts in the field, sufficient to demonstrate that the '996 parent application enables the claimed methods. The Examiner's Answer has disregarded this evidence, and instead has focused on one section of a single reference that was cited in the context of an obviousness rejection. Appellants summarize below evidence that has been presented, but either ignored or mischaracterized in the Examiner's Answer.

i) Evidence from the Specification

In the Appeal Brief, Appellants referred to various sections of the '996 parent application that provide guidance to one of ordinary skill in the art in practicing the claimed methods. The Examiner's Answer ignores the teachings of the specification regarding how to use the neurotoxic component. Indeed, the Answer completely fails to address several of the passages cited in the Appeal Brief. For the convenience of the Board, certain passages of the '996 parent application referenced in the Appeal Brief are reproduced below:

The Appeal Brief at page 7, second paragraph, refers to page 4, lines 9-12 of the '996 parent application with regard to purification of botulinum toxin and to page 7, lines 21-28 with regard to stabilizing and preserving botulinum toxin.

> Page 4, lines 9-12: Botulinum toxin is obtained commercially by establishing and growing cultures of in a fermenter and then harvesting and purifying the fermented mixture in accordance with known techniques.

> Page 7, lines 21-28: Where desired, tonicity adjusting agents such as sodium chloride, glycerol and various sugars can be added. Stabilizers such as human serum albumin may also be included. The formulation may be preserved by means of a suitable pharmaceutically acceptable preservative such as paraben, although preferably it is unpreserved.

The Appeal Brief at page 7, second paragraph, refers, *inter alia*, to page 7, lines 11-17 of the '996 parent application with regard to administration of the neurotoxic component to a patient.

> Page 7, lines 11-17: Preferably, the toxin is administered by means of intramuscular injection directly into a local area such as a spastic muscle, preferably in the region of the neuromuscular junction, although alternative types of administration (e.g., subcutaneous injection), which can deliver the toxin directly to the affected region, may be employed where appropriate.

The Appeal Brief at page 7, second paragraph, refers to page 9, line 21 to page 10, line 6 of the '996 parent application with regard to how a clinician would inject toxin in the treatment of strabismus.

> Page 9, line 21 to page 10, line 6: In each of the examples, appropriate areas of each patient are injected with a sterile solution containing the confirmation of Botulinum toxin [e.g., the neurotoxic component]. Total patient doses range from about 0.01 units to 460 units. Before injecting any muscle group, careful consideration is given to the anatomy of the muscle group, the aim being to inject the area with the highest concentration of neuromuscular junctions, if known. Before injecting the muscle, the position of the needle in the muscle is confirmed by putting the muscle through its range of motion and observing the resultant motion of the needle end. General anaesthesia, local anaesthesia and sedation are used according to the age of the patient, the number of sites to be injected, and the particular needs of the patient. More than one injection and/or sites of injection may be necessary to achieve the desired result. Also, some injections, depending on the muscle to be injected, may require the use of fine, hollow, teflon-coated needles, guided by electromyography. (Text in brackets added).

Rather than consider the guidance provided in the '996 specification, the Examiner's Answer makes only passing reference to the specification and does so in a conclusory fashion without providing any evidence to support the assertions. For example, the Examiner asserts that the '996 specification "did not disclose methods that one of ordinary skill in the art could utilize to render the pure toxin clinically effective."

Examiner's Answer at page 7, last paragraph. It is apparent that the Examiner has completely ignored the passages cited above from page 7, lines 11-17 and 21-28. As another example, the Examiner asserts that the "examples in the specification utilize DYSPORT and BOTOX." Examiner's Answer at page 16, last paragraph. The Examiner appears to have crafted this statement from whole cloth since the Examples in the specification do not state, nor have Appellants ever asserted, that DYSPORT or BOTOX were used in the Examples. In fact, contrary to the Examiner's assertion, the Examples **cannot** use only BOTOX and DYSPORT since both DYSPORT and BOTOX are type A toxins and several of the Examples explicitly refer only to botulinum toxin types B, C, D, E, F and G. As such, these Examples cannot utilize DYSPORT or BOTOX.

Thus, the Examiner's Answer has not fully and objectively considered the teachings of the '996 parent application with regard to enablement.

ii) Evidence from Published Scientific Articles

Appellants have provided objective evidence in the form of various published articles evidencing the knowledge in the art as of the filing date of the '996 application. The Examiner's Answer fails to fully and objectively consider the teachings of these articles regarding how to use the neurotoxic component. For the convenience of the Board, relevant sections of certain articles already of record are reproduced and discussed below.

First, Lamanna *et al.* reported in 1988 that hemagglutinin-free botulinum neurotoxin (i.e., neurotoxic component) could be formulated and injected intravenously. The Examiner's Answer addresses selected portions of the Lamanna *et al.* 1988 article, but fails to consider the entire disclosure. For example, Lamanna *et al.* state that:

> Page 70: G. Sakaguchi, University of Osaka Prefecture, provided a purified sample of type A toxin free of hemagglutinin... The toxins were dissolved in a sterilized phosphate-0.2% gelatin buffer (pH 6.2-6.7) **for storage and i.v. injection**... (emphasis added)
>
> Page 72: The crystalline toxin and the hemagglutinin-free toxin had the same qualitative effects on the heart, namely bradycadia and changes in the ECG.... On a weight to

> weight basis, hemagglutinin-containing toxin was less potent than the hemagglutinin-free toxin in causing cardiac changes... The crystalline toxin has a molecular weight of 900,000 and possesses 240 X 10^6 mouse LD_{50}/mg nitrogen while the hemagglutinin-free toxin has a molecular weight of 150,000 and possesses 500 X 10^6 mouse LD_{50}/mg nitrogen...

Evidence Appendix K. Thus, Lamanna *et al.* demonstrate that the neurotoxic component can be stabilized and that the stabilized neurotoxic component is suitable for intravenous injection. The Examiner clearly fails to consider Lamanna *et al.* in its entirety, stating that:

> "Lamanna et al. disclose formulation and storage of the botulinum toxin neurotoxic component. However, Lamanna et al. does [sic] not resolve the issue at hand. Namely, how does one of ordinary skill in the art go about making the pure neurotoxin less labile so it could be used in clinical settings?"

Examiner's Answer at page 18, last paragraph. Clearly, the Examiner has acknowledged that part of Lamanna *et al.* in which the preparation of a stable, pure (i.e., hemagglutinin-free) neurotoxic component is reported, but has ignored that part of Lamanna *et al.* in which the neurotoxic component was **actually used** for intravenous injection.

Second, the Examiner's Answer dismisses a review article by DasGupta because it was published in 1994, after the filing date of the present application. The DasGupta review, however, discusses in detail numerous scientific articles going back to 1946, several of which address stability of the neurotoxic component. For example, the DasGupta review states:

> Pages 31-32: The NT [neurotoxin] (mol. wt. ~150,000) isolated from the complex by ion-exchange chromatography, first reported in 1966 [citing DasGupta *et al.*, 1966] and now routinely prepared in various laboratories [citing Sugii *et al.*, 1975 and Tse *et al.*, 1982] has stable activity; Williams *et al.* [citing Williams *et al.*, 1983] have found that the homogeneous preparation of type A NT, stored at 4°C in 0.15 M TRIS-HCl buffer, pH 7.9, is stable for several months. The pure preparations of NT types A and E at very low concentrations (such as 1 X 10^{-10} M and lower) in physiological buffers, with and without added gelatin or serum albumin, are highly active...

Evidence Appendix G. Thus, DasGupta indicates what one of ordinary skill in the art would have known as of the filing date of the '996 parent application, as reflected in articles published in 1966, 1975, 1982 and 1983. For example, DasGupta refers to a 1983 article by Williams *et al.* showing that the neurotoxic component was stable for several months after isolation, and retained activity with or without added stabilizers.

The Lamanna and DasGupta publications provide evidence that at the time the '996 parent application was filed, purified neurotoxic component had been isolated, formulated, and stored in stable form. Moreover, these publications provide evidence that the neurotoxic component is sufficiently stable and active to be administered intravenously.

The Examiner's Answer has given no weight to the evidence from these published articles, asserting that:

> "they do not sufficient [sic] present evidence to how one of ordinary skill in the art would make the pure toxin clinically viable."

Examiner's Answer at page 17, last paragraph.

The Examiner has failed to indicate why the evidence from these published articles is insufficient. Instead, the Examiner continues to place singular emphasis on a portion of a review article by Schantz *et al.* that teaches away from the claimed methods, asserting that Schantz *et al.* disclose that the neurotoxic component is too labile to be used in a clinical setting. Examiner's Answer at page 17, first paragraph. The published articles mentioned above, however, indicate that the neurotoxic component is <u>not</u> labile and can be made into a storage stable formulation. The Examiner is improperly using Schantz *et al.* in isolation and is disregarding the weight of evidence from other published articles in the field that contradict Schantz *et al.*'s isolated statement.

Third, the Examiner misquotes Appellants, and uses the fictitious quote to support his enablement rejection in view of the Schantz et al. article. Specifically, the Examiner continues to quote the Appellants as stating that "[A]t the time of the filing of the present application, one of ordinary skill in the art would not consider using only the

purified botulinum toxin component of botulinum toxin in clinical settings." Examiner's Answer at page 17, last paragraph. As indicated in the Appeal Brief, Appellants made no such statement. Appellants actually stated that "[A]t the time of the filing of the present application, ***one of ordinary skill in the art would not consider the teachings of the Tse reference regarding the use of pure botulinum toxin to be relevant to clinical treatment***..." (emphasis added). See Response dated September 26, 2006. This statement was made in response to an obviousness rejection to show that prior to Appellants' disclosure, one of ordinary skill in the art would not be motivated to combine the teachings of Tse with other references cited by the Examiner.

As discussed in more detail in Section C below, teaching away is probative of obviousness, but is not the primary question bearing on enablement. Thus, even had the Examiner correctly quoted Appellants, Appellants' statement would still not be the primary question bearing on enablement, and certainly would not rebut the weight of the other scientific articles demonstrating that one of ordinary skill in the art would have been able to use pure the neurotoxic component in a clinical setting without undue experimentation as of the filing date of the '996 parent application.

By misquoting Appellants, applying an erroneous legal standard, and disregarding the teachings of DasGupta, Lamanna *et al.*, and other articles of record, it is clear that the Examiner has not fully and objectively considered the evidence from the majority of published articles in this field in denying the present application benefit of priority to the '996 parent application for lack of enablement.

iii) Declaratory Evidence

Appellants have provided further objective evidence of enablement in the form of sworn Declarations from acknowledged experts in the field, Dr. Mitchell Brin and Dr. Leonard Smith. Dr. Brin presented his opinions in paragraphs 15 and 17of his Declaration, based on evidence from the '996 application and the published literature as set forth in paragraphs 16 and 18. Evidence Appendix F. Dr. Smith presented his opinions in paragraphs 15 and 17 of his Declaration, based on evidence from the '996

application and the published literature as set forth in paragraph 15(a), (b) and (c), and paragraph 17 (a), (b) and (c). Evidence Appendix J.

The Examiner's Answer, however, has all but disregarded the Brin and Smith Declarations. Regarding the Brin Declaration, the Examiner states that:

> "The Declaration by Dr. Brin does not provide any evidence to counter the contentions raised by Schantz *et al.* While one of ordinary skill in the art may be able to make the neurotoxic component the Declaration does not set forth how one of ordinary skill in the art can use the toxic component as claimed to treat the disorder as claimed..." (emphasis added).

Examiner's Answer at paragraph spanning pasges 19 and 20. In making this statement, the Examiner has clearly ignored paragraph 18 of the Brin Declaration, in which Dr. Brin outlines evidence upon which he based his opinion.

Moreover, the Examiner states that "the [Brin] Declaration does not set forth any evidence, between the date of Schantz *et al.* and the filing date of the present invention, to rebut how at the time of the filing of the present application, one of ordinary skill would consider using only the purified botulinum toxin... in clinical settings, given the teaching of Schantz *et al.*" Examiner's Answer at page 20, first paragraph. Aside from highlighting the Examiner's fixation on the unsupported opinion of Schantz *et al.*, this statement also demonstrates another of the erroneous legal standards applied by the Examiner. There is simply no requirement under US patent law that Appellants must submit evidence dated after Schantz *et al.* to rebut the Examiner's assertion of non-enablement of the claimed methods.

Even under this erroneous legal standard, Appellants have in fact provided evidence between the publication date of Schantz *et al.* and the filing date of the '996 parent application that challenges the opinion of Schantz *et al.* In his Declaration, Dr. Smith referred to a 1993 paper by Lamanna *et al.* (included as Evidence Appendix I) reporting that purified, stable neurotoxic component was administered to several mammalian species, and such administration achieved a physiological effect. The Examiner has apparently ignored this evidence as well.

It is revealing to consider the Examiner's stated rationale for elevating the unsupported opinion of Schantz *et al.* to scientific fact. The Examiner asserts that the Schantz reference discloses "dilution at low concentrations, pH of greater than 7.3 the neurotoxin is liberated as the basis for its conclusions." Examiner's Answer at page 19, middle paragraph. This statement, however, fails to provide a basis for anything other than the fact that the neurotoxic component can be liberated. As described above, methods of isolating the neurotoxic component were well known prior to the filing date of the '996 parent application. This statement, however, does not lead to the Examiner's conclusion, which is used as the primary basis for the enablement rejection, that the neurotoxic component is too labile to be used in a clinical setting.

In short, the Examiner has given dispositive weight to the opinion of Schantz *et al.*, and given little or no weight to the sworn Declarations of Drs. Brin and Smith and the evidence and facts upon which they base their opinions. As such, it is clear that the Examiner has not fully and objectively considered the Brin and Smith Declarations.

C) The Examiner has Confused the Legal Standards for Enablement and Obviousness

The Examiner has applied an erroneous legal standard for enablement, placing dispositive weight on a single prior art reference that teaches away from the claimed methods and confusing the legal standard for enablement with the legal standard for non-obviousness. As Appellants have previously explained, the Federal Circuit stated in Singh v. Brake that "whether or not a reference 'teaches away' from a claimed invention... [is] relevant in determining whether a claimed invention would have been obvious, but [is] not the primary [question] bearing on enablement." 317 F.3d 1334, 1346, 65 USPQ2d 1641, 1650 (Fed. Cir. 2003). The Examiner's Answer cites no legal authority that contradicts Singh v. Brake, merely noting that the case was cited in the Appeal Brief.

D) Other Errors in the Examiner's Answer

Finally, there are a number of other misstatements and errors in the Examiner's Answer, in addition to those mentioned above. In the interest of maintaining a clear and accurate record, Appellants wish to correct some of these other errors.

In discussing the Wands factors on page 5, lines 5-6 of the Answer, the Examiner incorrectly asserts that the nature of the invention is directed to use of botulinum toxin. The claimed methods actually recite use of the **neurotoxic component**.

On page 12, lines 1-5 of the Examiner's Answer, the Examiner quotes Appellants as stating that the specification need not necessarily describe every possible variant of a claimed invention. In fact, Appellant was directly quoting from the Federal Circuit decision in AK Steel Corp v. Sollac, 344 F.3d 1234, 1244 (Fed. Cir. 2003).

On page 13, lines 14-16 of the Answer, the Examiner asserts that the disclosure simply gave a general teaching regarding Botulinum toxin since the term "Botulinum toxin" is generic. Appellants have never asserted that the specification gives only a general teaching regarding Botulinum toxin. Appellants have pointed to numerous sections of the '996 parent application that enable use of the neurotoxic component. Moreover, Appellants previously overcame a rejection based on alleged lack of written description for the neurotoxic component. Thus, the specification clearly provides far more than a general teaching regarding Botulinum toxin.

E) Conclusion

In summary, Appellants have put forth a variety of evidence that supports a conclusion of enablement, including explicit teachings from the specification, publications that indicate what would have been known to one of ordinary skill, and sworn Declarations from distinguished experts in the field. In contrast, the Examiner's Answer places singular and dispositive weight on a statement made by Schantz *et al.*, which statement is contradicted and rebutted by substantial evidence. Moreover, the Examiner continues to apply several erroneous legal standards in rejecting the presently pending claims.

Both the law and the facts are contrary to the Examiner's position. The specification, viewed objectively, clearly enables one of ordinary skill to use the claimed invention. Appellants respectfully request that the Board reverse the denial of priority of pending claims 1-2, 4-5, 29, 47, 63 to the '996 application under 35 U.S.C. §120 on the basis of lack of enablement under 35 U.S.C. §112, first paragraph.

II. Rejection Under 35 U.S.C. § 103 Over Balkan *et al.* or Han *et al.* in View of Tse *et al.*, Kohl *et al.* and Aoki *et al.*, and in View of Kohl *et al.*, Aoki *et al.* and Aoki *et al.*

Appellants maintain the arguments presented in the Appeal Brief. In summary, neither Kohl *et al.* nor Aoki *et al.* are prior art, and even if they were prior art their combination with the other cited references would not render the presently pending methods obvious. The Board is requested to reverse the rejection of pending claims 1-2, 4-5, 29, 47, 63 as being obvious over the cited references.

Appellants are also submitting with this Reply a Request for Oral Hearing under 37 C.F.R. §41.47.

Please apply any charges or credits to Deposit Account No. 01-0885.

Respectfully submitted,

Date: February 24, 2009

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